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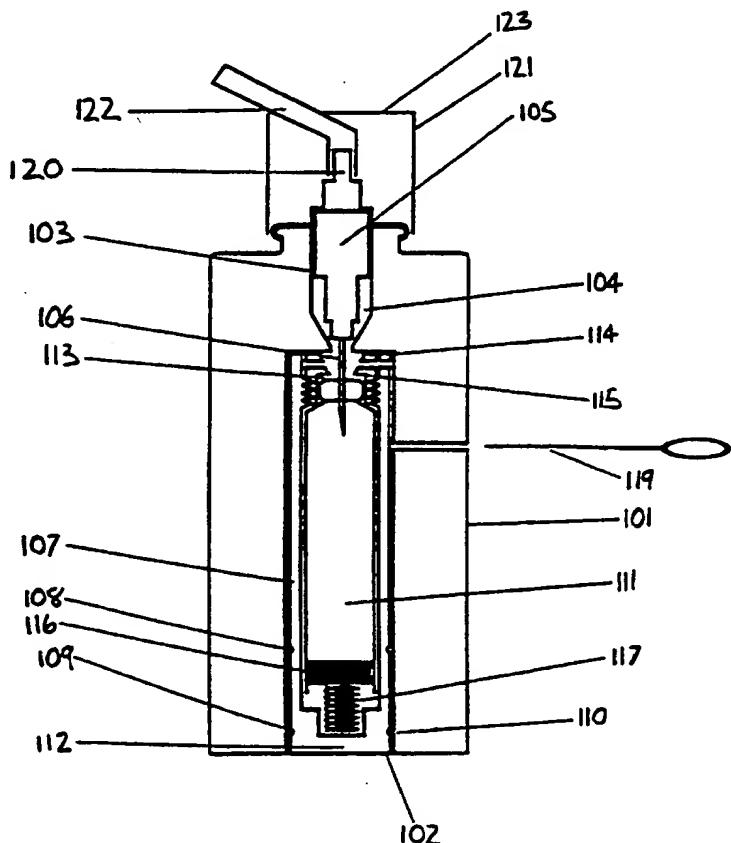
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(54) Title: SPRAY APPLICATOR

(57) Abstract

A multi-dose spray applicator is disclosed for dispensing a pharmaceutical from a sealed container, said applicator comprising means for holding the container, a manually operable metering pump for delivering said pharmaceutical as a nasal spray and a hollow needle associated with said pump for penetrating a membrane sealing said container and dispensing the pharmaceutical through the pump, said container having a movable wall or plug which is movable to displace liquid from the container as it is dispensed by the pump.



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SPRAY APPLICATOR

This invention relates to spray applicators, particularly for dispensing pharmaceutical substances. One established method of dispensing pharmaceuticals is by spray e.g. as a nasal or oral spray. This method has the advantage as compared with sub-cutaneous or intravenous injection that it is easier for a patient with poor co-ordination or muscular weakness to administer the pharmaceutical himself. In the past, containers fitted with a pump or aerosol packaged products have been employed. However, these methods have proved to be unsatisfactory for packaging pharmaceuticals which are sensitive to substances in the atmosphere, such as compounds which degrade by contact with water or oxygen.

It is, therefore, one object of the present invention to provide an applicator for dispensing pharmaceuticals in the form of a spray, which minimises contact with atmospheric components until the product is dispensed.

According to one aspect of the present invention, there is provided a spray applicator for dispensing a pharmaceutical from a sealed container, said applicator comprising means for holding said sealed container, a manually operable pump for delivering said pharmaceutical as a nasal spray and a hollow needle associated with said pump for penetrating a membrane sealing the container and dispensing the pharmaceutical through the pump.

The applicator of the present invention is particularly designed for dispensing pharmaceuticals which are sensitive to oxygen or water. One example of such a compound is apomorphine hydrochloride (or other pharmaceutically acceptable salt) which is widely used in the treatment of Parkinson's disease. For such use, apomorphine is conveniently applied as a

nasal spray and is rapidly absorbed through the nasal membrane. The spray applicator may, however, be adapted for other purposes, e.g. for applying a spray to the mouth and for dispensing other pharmaceuticals via the mouth or nose, particularly for treating the mouth, nose and lungs.

The pump component of the applicator may be constructed as a metering pump so that on actuation of the pump, a metered dose of the pharmaceutical is sprayed into the patient's nose or mouth.

Preferably, the applicator includes means for moving the needle towards the membrane automatically on actuation or just prior to actuation of the pump. For example, depression of the pump system may cause the needle to move towards and penetrate a membrane sealing the container in which the pharmaceutical is packaged.

In order to prevent the device from being actuated unintentionally, the applicator may include a removable device such as a clip, ring or tag which prevents the needle penetrating the membrane or prevents, respectively, means carrying the needle and sealed container from coming together until the applicator is intended to be used.

When the needle penetrates the membrane over the end of the vial, the contents remain substantially sealed with respect to the atmosphere so that air cannot enter the vial.

In order to allow the liquid within the pharmaceutical container to be displaced without the need to introduce air or other gas into the sealed vial, the pharmaceutical container preferably has a wall or plug which is movable to displace liquid as it is pumped out of the container by the pump device. Such moveable wall or plug may be urged inwardly by a spring or other mechanical

device so as to assist priming the pump, although the spring is not essential. The container may be constructed as a collapsible container, such as a tube, by making the walls from a flexible material such as a plastics sheet material.

One pharmaceutical application of the spray applicator is for dispensing compounds for controlling Parkinson's Disease. Patients suffering from Parkinson's Disease often have difficulty in manipulating devices for administering their medication. A further feature of the applicator of the invention is to provide a dispensing cap in which the outlet from the pump is angled obliquely, thus providing a platform on the cap of the applicator which enables the patient to operate the pump conveniently with his thumb.

Two embodiments of the present invention will now be described with reference to the accompanying drawings, which are partly schematic.

In the accompanying drawings:-

Figure 1 is a longitudinal section through the applicator in assembled condition,

Figure 2 is a perspective view of a clip for preventing the needle penetrating the sealed container,

Figure 3 shows the components of the applicator in a disassembled state,

Figure 4 is a schematic view showing an alternative method of actuating the pump,

Figure 5 is a longitudinal view in section of a second embodiment of the applicator in its "use" position;

Figure 6 is a similar section through the applicator shown in Figure 5, but in its "rest" position:

Figures 7 shows the disassembled components of the applicator shown in Figures 5 and 6; and

Figures 8A and 8B are two perspective views of a modified dispenser.

Referring to Figures 1 to 4 of the accompanying drawings, the nasal applicator comprises a container (1) shaped to receive a sealed vial (2) into which the pharmaceutical is packaged. Vial (2) is of a type which is currently used in the pharmaceutical industry for packaging injectable materials. The vial comprises a glass or plastics tube (3) having a lower end which is closed with a rubber or plastic bung or plug (4). The upper end of the vial has membrane (5) which is designed to be penetrated by a hypodermic needle for removing the contents. After penetration of the membrane the membrane is sufficiently elastic to close around the needle and seal itself against inadvertent escape of liquid or escape under the pressure arising during pumping of doses of liquid from the container. The membrane is preferably a rubber or rubbery plastics material. Vial (2) is designed to be a multi-dose container so that as liquid is removed from the vial (2), plug (4) moves upwardly to displace the liquid so removed. A spring (6) may be employed to assist this action and/or priming of the pump but is not essential. At its upper end, container (1) is threaded to receive a cap (7) and a pump holder (8) is mounted for axial sliding movement on the neck (9) of the container (1). Crimped onto the neck (10) of the pump holder (8) is a pump (11) and mounted on the upper end of the pump is a nasal actuator and overcap (12) and (13) respectively. Pump (11) is of the kind conventionally used for pumping pharmaceuticals from closed containers. The pump may be an airless mechanical pump with or without a dosing device such as those manufactured by Perfect-Valois or their parent

company Valois Step under model No. 'VP 7'. An example of a metering pump of this kind is also described in WO 95/09054.

The lower end of the pump (11) has a tubular portion (14) to which a hollow needle (15) is attached either internally or externally, e.g. by means of a luer-type connection.

The applicator works in the following manner. Cap (13) which is a press fit of actuator (12) is removed and the actuator pressed down by placing the fingers on ledges (16). This causes pump holder (8) to move downwardly until needle (15) penetrates the membrane (5) and enters the liquid contained in vial (2). Continuing downward pressure causes the pump to take in a dose of the pharmaceutical and to spray the dose through the nasal actuator (12). On release of such finger pressure, needle (15) remains in the vial with the membrane sealing around the needle to prevent escape of liquid between the outer surface of the needle and the membrane. This is because the underside 26 of the cap engages with the recess 25 of the cap 8 or the annular projection 27 engages in the groove 21. The piston (not shown) within pump 11 is returned to its initial position by a return spring within the pump housing 11. This aspirates liquid into the pump ready for dispensing the next dose from the vial. Further doses of liquid can be pumped from the vial by the patient as required by pressing on the ledges 16.

In order to prevent the applicator from being inadvertently actuated, a removable clip (20) may be fitted into a groove (21) in the neck (9) of container (1). The clip (20) may be manufactured from a springy plastics material so that it is readily removed by pulling the tag or ring which is attached to it. When the clip (20) is in place, however, its thickness or an abutment

protruding from it, prevents the pump holder moving down the neck (9) sufficiently far to allow the hollow needle to penetrate the membrane (5).

Figure 4 shows an alternative way of depressing the actuator (12) for patients who have very poor co-ordination or muscular power. In this modification, the container (1) may be gripped by a holder (30) having a lever (31) mounted thereon. Lever (31) has an arm (32) which is shaped to press onto shoulders (16) of the nasal actuator (12). By operating lever arm (33), the patient is able to actuate the applicator with minimum mechanical force.

It will be appreciated that various modifications can be made to the applicator in accordance with the invention. For example, the holder may be formed with a threaded, removable base for introducing the vial and the neck (7) may be formed integrally with the body (1). The pump unit may be crimped downwardly onto the neck of the holder and be arranged to be movable downwardly to permit the needle to enter the membrane (5).

Conveniently, most of the components of the applicator may be manufactured from plastic materials. The holder (1) may, for example, be made from a clear plastics material so that the patient can see whether the vial is empty. In the case of apomorphine, the pharmaceutical turns green after exposure to atmospheric oxygen. Once the contents of the vial are observed to have changed to a green colour which is sufficiently deep (as indicated by a shade chart on the applicator or packaging), to indicate that the pharmaceutical is no longer effective. An important aspect of the application of this invention is that the pharmaceutical in the vial remains sealed from the atmosphere until the patient uses the applicator for the first time.

Figures 5, 6, 7, 8A & 8B show modified applicators which include a number of modifications but work in a similar fashion to the applicator shown in Figures 1 to 4.

Referring to Figures 5, 6 and 7, the modified dispenser comprises an outer hollow component (101) forming one part of a container, preferably moulded from plastics material. In the embodiment shown in these Figures, the pump (105) is the same kind of metering pump as already described in connection with Figures 1 to 4. Also, the vial (111) is essentially as described in relation to the embodiments of Figures 1 to 4. The differences concern the container for the vial and the nozzle through which the product is dispensed. Component (101) is open at one end (102) and at its other end (103) is formed with a mouth and throat (104) for receiving a dosing pump (105). Pump (105) is preferably crimped into the mouth (104) of component (101), e.g. with an aluminium closure ferrule. A hollow needle (106) is fitted to the pump (105).

A second component (107) of the container is slidably received in the tubular hollow part of component (101). Again, the second component is conveniently moulded from plastics material. Component (107) is formed with two longitudinally spaced grooves (108) and (109) and the inside of the component (101) is formed with a corresponding annular ring or projection (110).

Component (107) is formed with a tubular cavity for receiving a vial (111) and has a closed base (112) and a neck (113). Vial (111) is retained within the component (107) by a threaded cap (114) which engages with corresponding threads on the inside of the neck of the component (107). Alternatively, the cap (114) may be a friction fit in the neck of component

(107) or one of the components may have lug(s) which engage with groove(s) or recesses. In use, the shoulder of the vial (111) will abut against the cap (114) or the neck will abut against a ledge (115). However, for clarity a slight gap is shown in the drawing. Vial (111) is a tube open at its lower end but includes a sealing plug (116) (preferably of elastomeric material). Plug (116) is preferably in contact with a spring (117) tending to urge the plug towards the neck of the vial.

As shown in Figure 6, the cap (114) is formed with a slot (118) into which a guard strip (119) slides. Guard strip (119) passes through slots (118A & 118B) in components (101 & 107) which are aligned with slots (118) in cap (114). The width and toughness of strip (119) is such that it would be difficult for needle (106) to penetrate it and reach the membrane across the neck of vial (111).

Pump (105) has an outlet tube (120) depression of which causes the pump to operate. Tube (120) is received within a nasal spray head (121) which has a dispensing nozzle (122) connected to the tube (120). Nozzle (122) extends obliquely to the centre line of the dispenser so as to provide a convenient ledge (123) for the patient to apply finger pressure to operate the device.

The dispenser shown in Figures 5, 6 and 7 works in the following manner. In the position shown in Figure 6, the projection (110) engages in groove (108) and releasably retains the inner component in relation to the outer component (101) in the position shown in Figure 6.

When it is desired to use the dispenser, the guard strip (119) is pulled out by pulling on the ring (120). The dispenser can then be operated by

pressing the base (112) on a flat surface and pressing, e.g. with the thumb on the ledge (123). This causes the inner component to be pressed into the outer component (101) and the needle to penetrate the membrane (124) across the neck of the vial. At the same time, the annular projection (110) engages in the groove (109) thus retaining the component (107) within the component (101). For this purpose, projection (110) can be made to be a better fit in groove (109) than in groove (108) so that it is easier to dislodge projection (110) from groove (108) than groove (109).

It has been found that a needle which has a very slight or no taper at all is best employed. This is because needles with a long taper tend to allow the contents of the vial to spray out as the needle begins to penetrate the membrane. However, conventional needles may be employed.

The walls of the components (101,107) may be transparent or include a window. This arrangement enables the contents of the vial to be checked, e.g. to see if the vial contains sufficient liquid for one more treatment or, in the case of some medicaments, to check the appearance of the contents since this can undergo a colour change which may indicate it is no longer effective.

Instead of having a spring such as the spring (6) shown in the embodiments of Figures 1 to 3, a projection is moulded on the base (108). This projection bears on the plug (112) so that when the applicator is initially activated, the plug is urged upwardly and primes the pump.

Figures 8A and 8B show external perspective views of a modified dispenser. In this embodiment, the vial (not visible) is contained within a body 400 which may be formed from inner and outer components similar to components (101,107) in Figures 5 and 6. A guard strip (401) is received in a

slot (402) and prevents the dispenser being actuated inadvertently. A spray head (403) is fitted to the discharge tube of the pump and provides a platform (404) for applying finger or thumb pressure to operate the pump. Nozzle (405) terminates in a discharge outlet which may incorporate various outlet designs to vary the spray pattern. A closure cap (405) may be fitted over the nozzle to protect the nozzle for storage and transport.

CLAIMS:-

1. A multi-dose spray applicator for dispensing a pharmaceutical from a sealed container, said applicator comprising means for holding the container, a manually operable metering pump for delivering said pharmaceutical as a nasal spray and a hollow needle associated with said pump for penetrating a membrane sealing said container and dispensing the pharmaceutical through the pump, said container having a movable wall or plug which is movable to displace liquid from the container as it is dispensed by the pump.

2. An applicator as claimed in claim 1, which includes means for moving the needle towards the membrane on initial actuation of the pump.

3. An applicator as claimed in claim 2 which includes a removable device to prevent the needle penetrating the membrane until the applicator is intended to be used.

4. An applicator as claimed in claim 3 in which the safety device comprises a shield located between the membrane and the needle, said shield being movable to an inoperative position when the applicator is intended to be used.

5. An applicator as claimed in claim 3 in which the safety device comprises a locking means which in its operative position prevents a component carrying the pump towards the container to an extent that the needle penetrates the membrane.

6. An applicator as claimed in any one of the preceding claims wherein the plug is movable into the container under the influence of a spring.

7. An applicator as claimed in any one of the preceding claims in which the pump is primed by movement of the needle into the container.

8. An applicator as claimed in any one of the preceding claims wherein the means for holding the container comprises a housing, said housing comprising a base part for holding said container and a top part for holding the pump, the top and base parts being relatively movable to allow the needle to penetrate the membrane.

9. An applicator as claimed in claim 8 wherein the base part is slideable within the top part and the two parts include co-operating means for holding them together with the end of the needle within the container and the membrane forming a seal around the needle.

10. An applicator as claimed in claim 9 wherein the co-operating means include at least one resilient finger on one part which is engageable in a recess in the other part.

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FIGURE 1

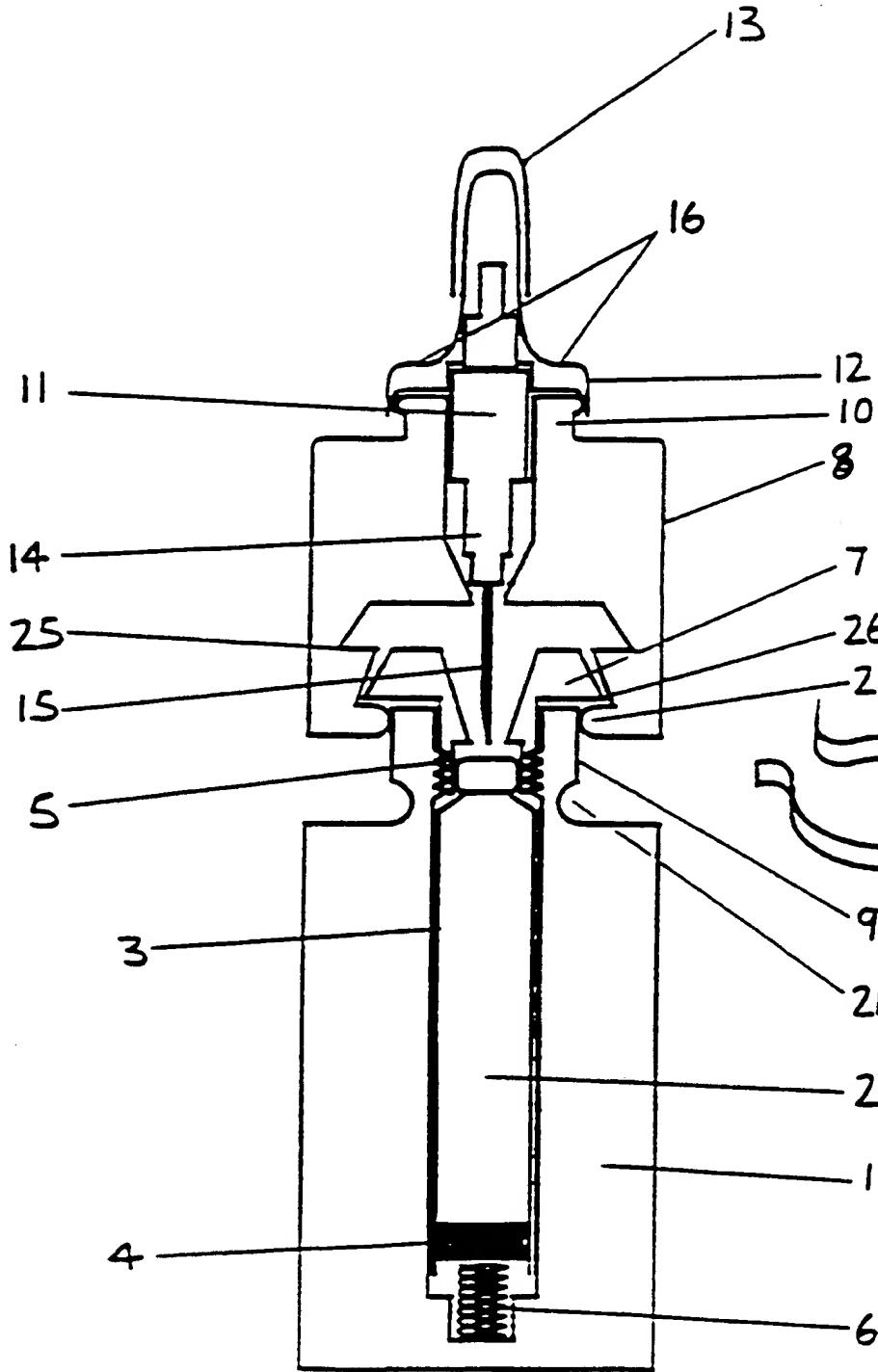
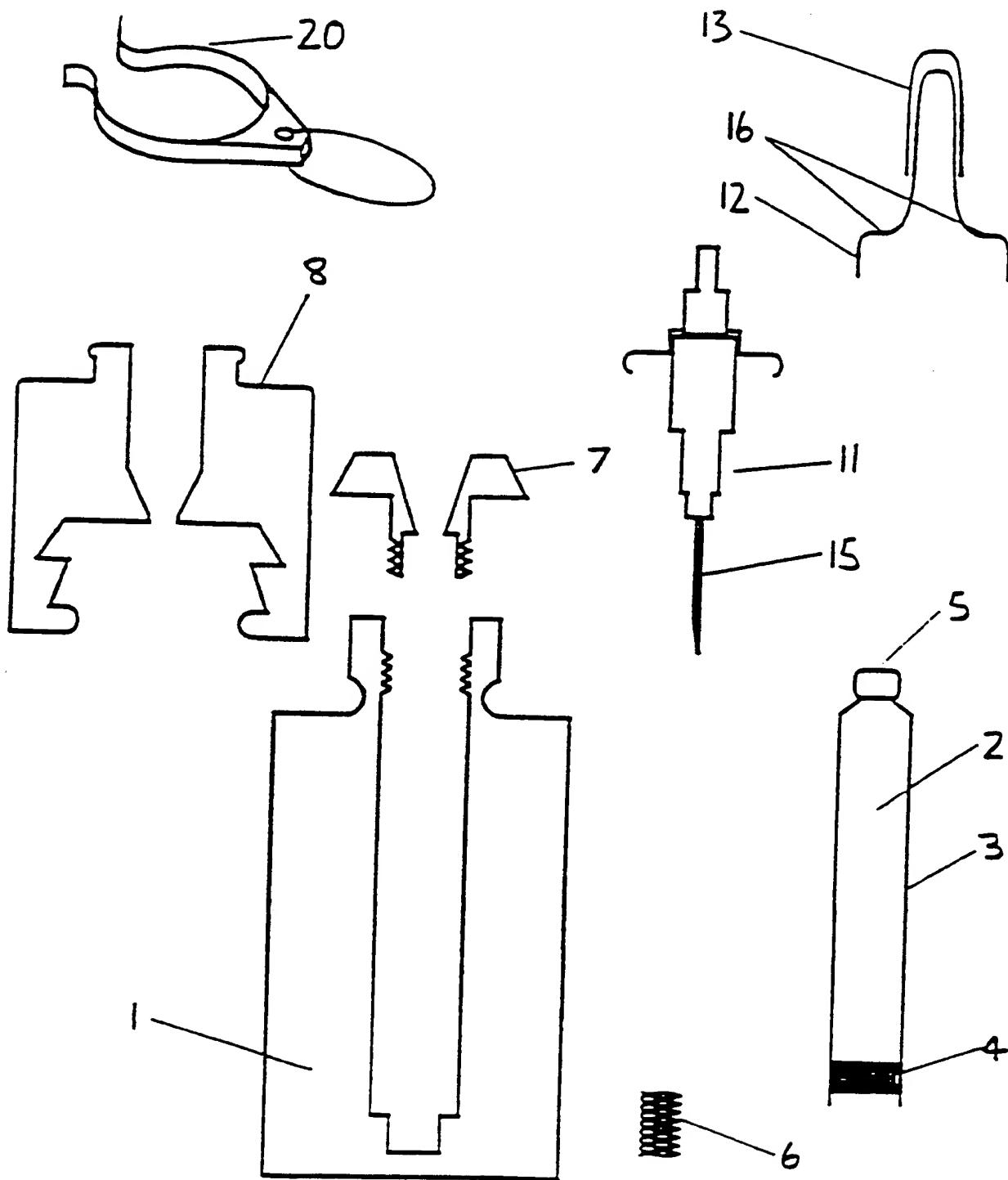


FIGURE 2

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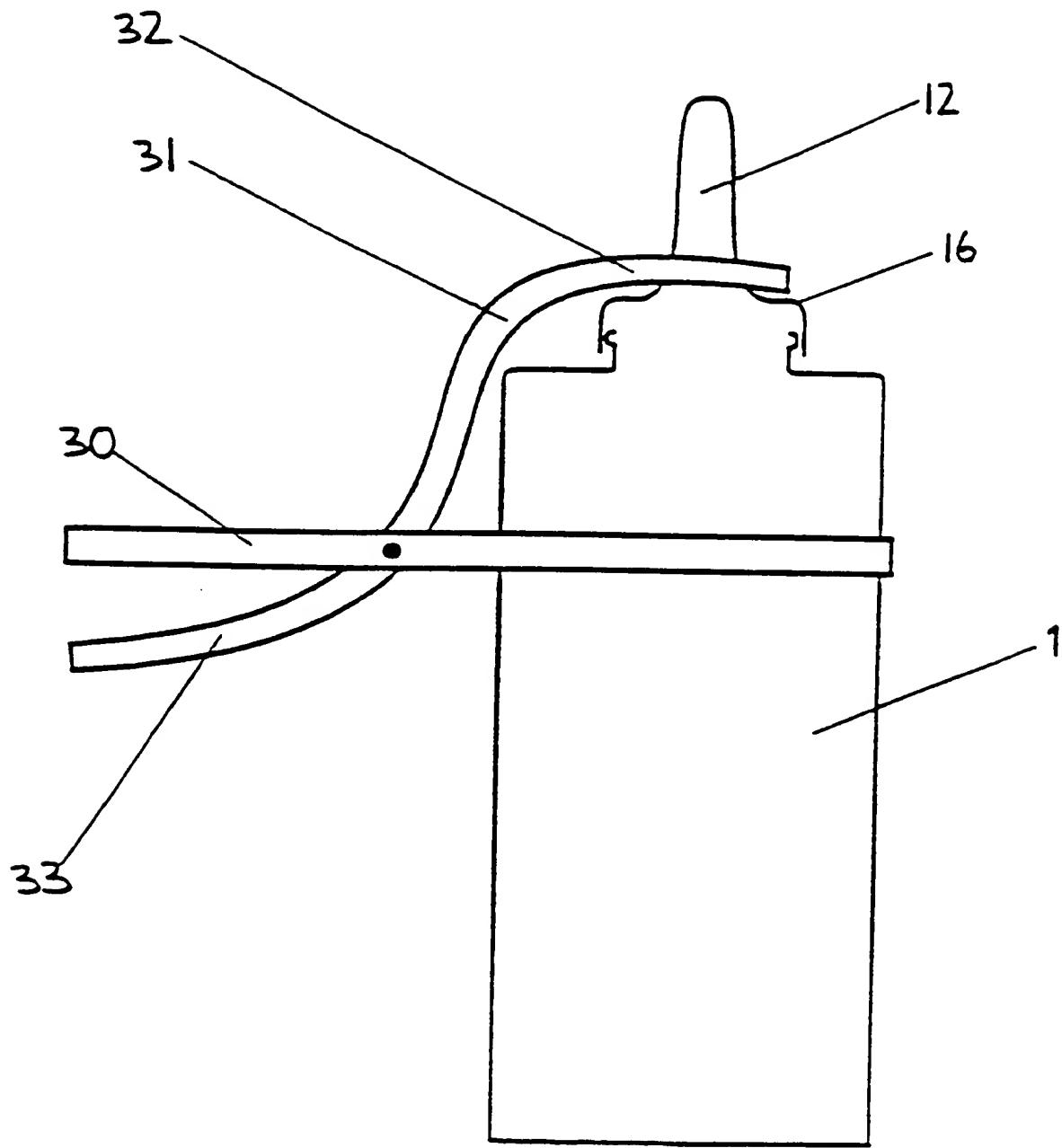
FIGURE 3



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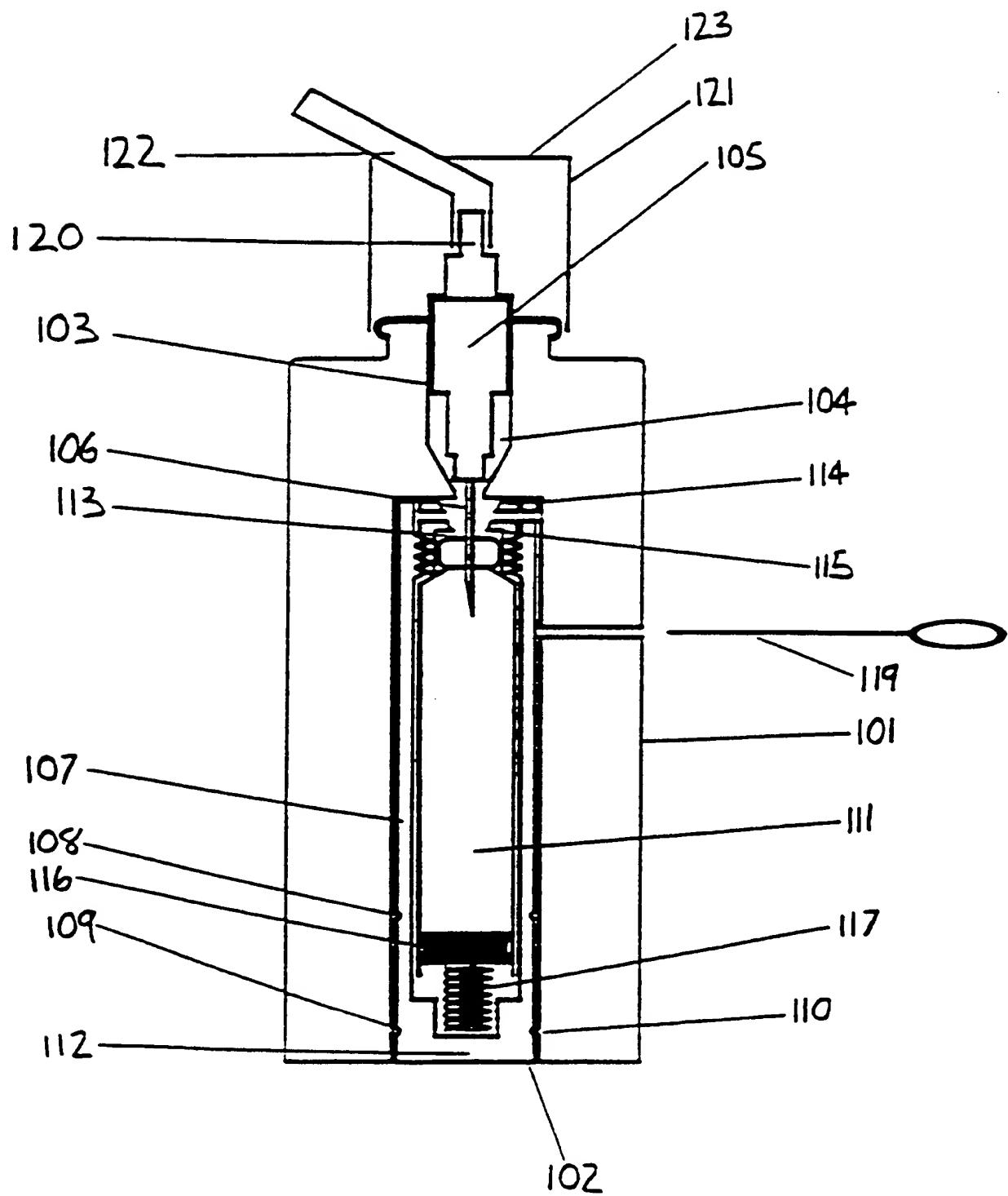
FIGURE 4



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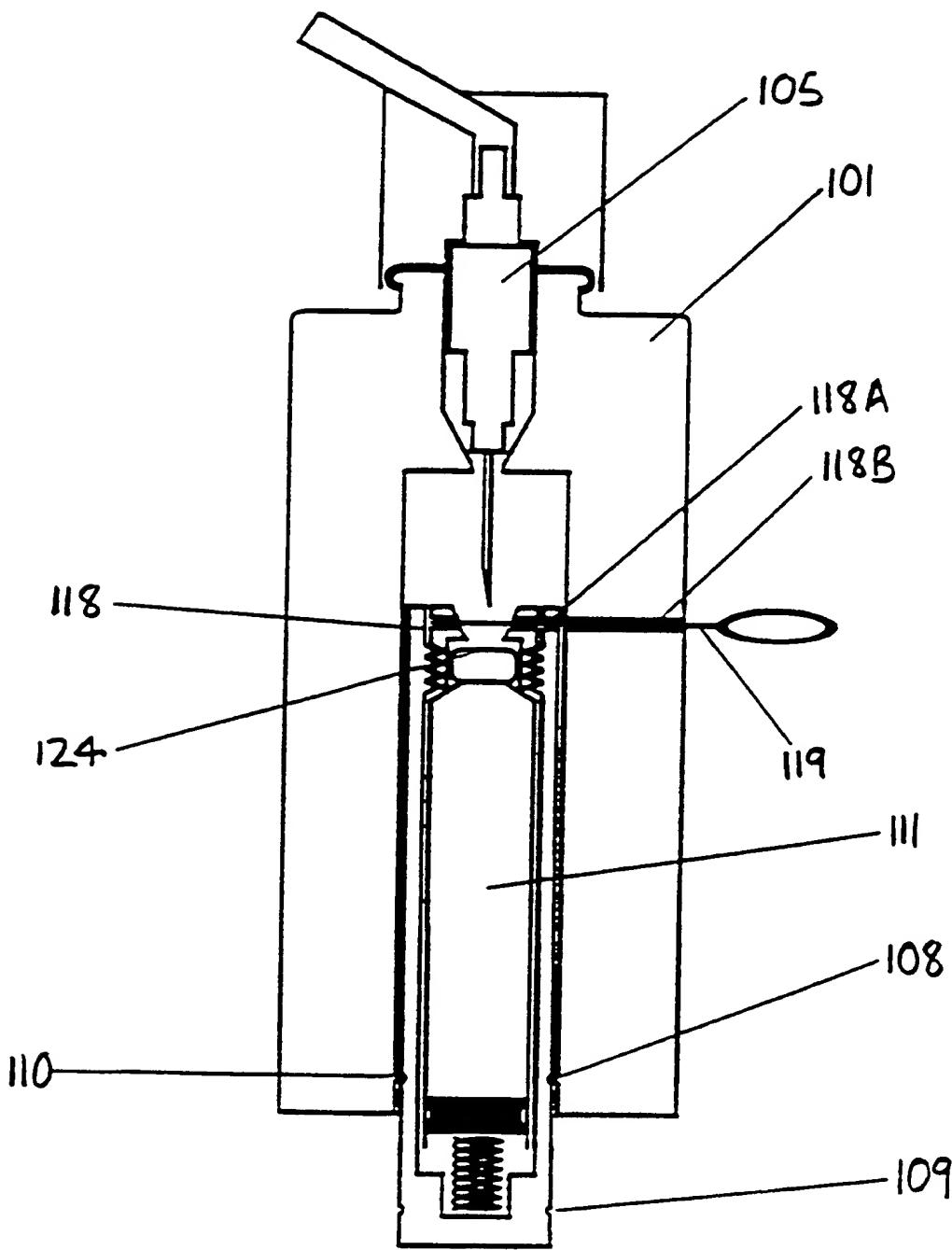
FIGURE 5



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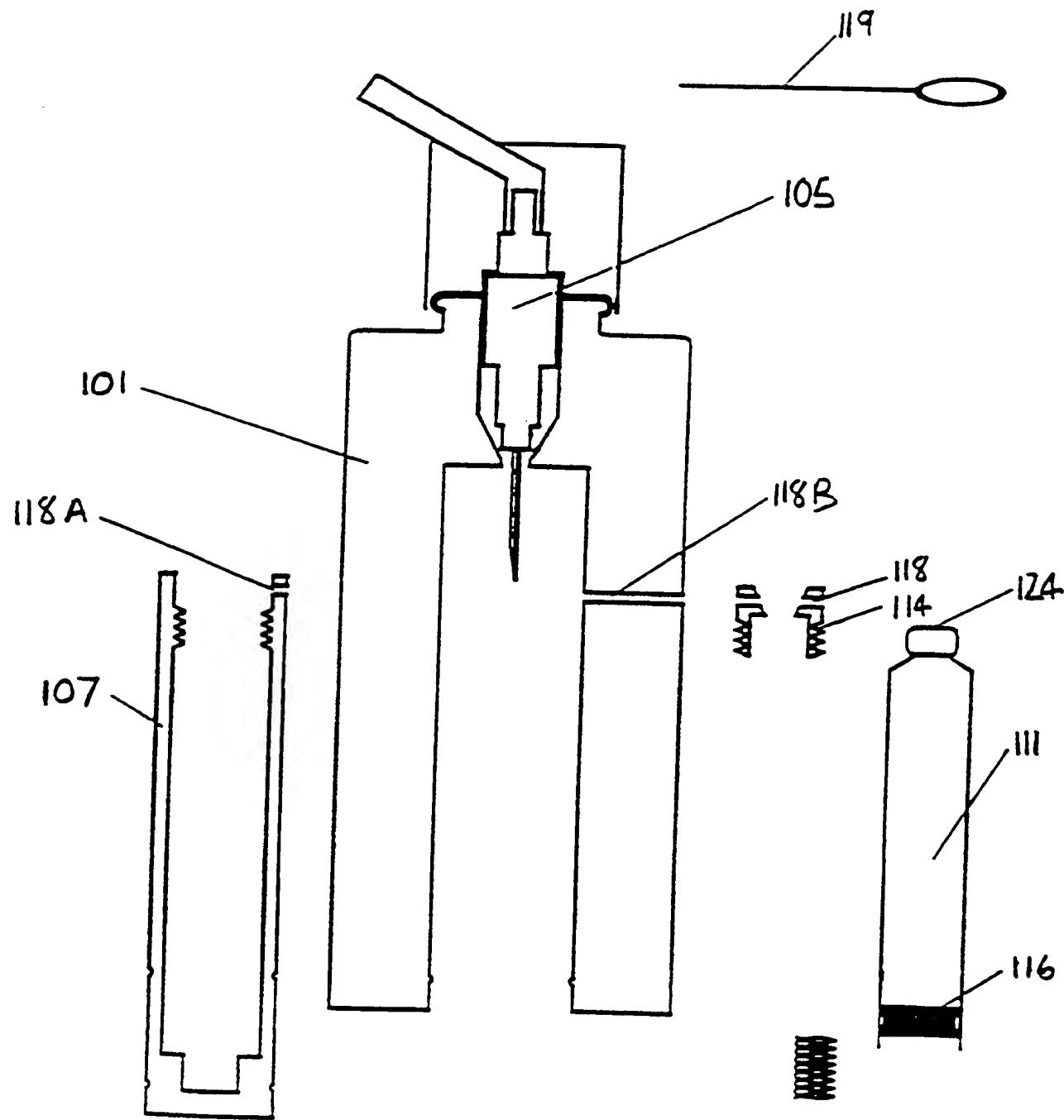
FIGURE 6



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FIGURE 7



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Figure 8A

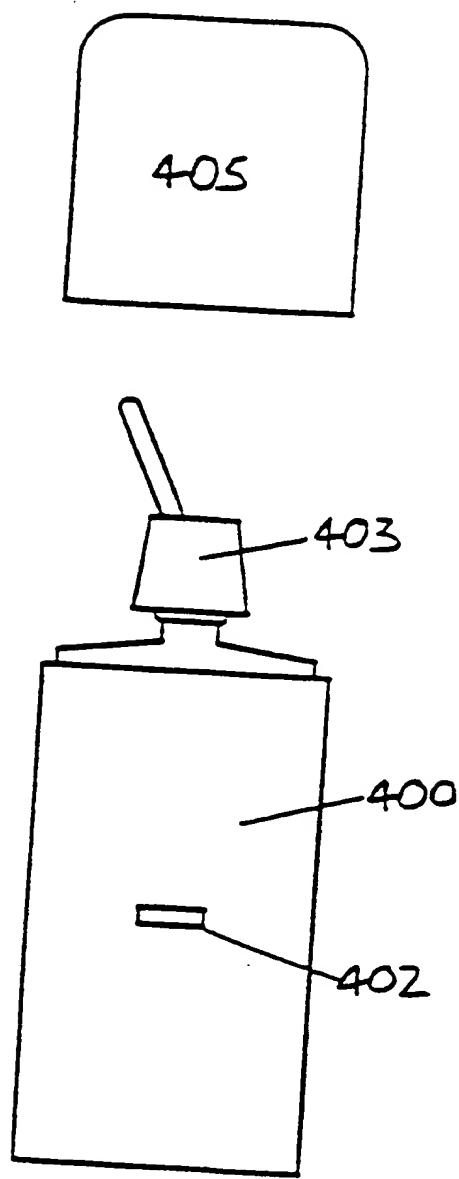
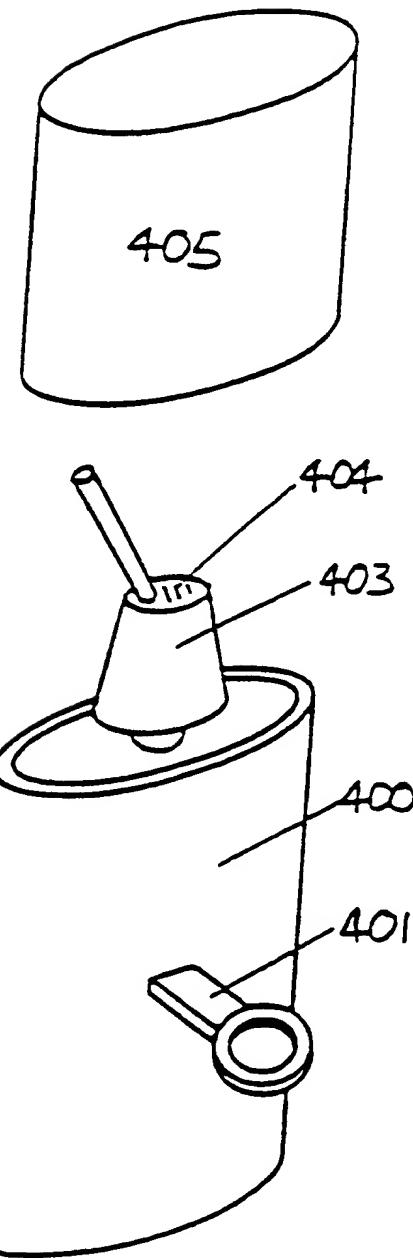


Figure 8B



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M15/00 B05B11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M B05B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 770 323 (DEBARD) 13 September 1988 see column 3, line 3 - line 56; figures 1-4 ---	1-3,5, 7-9
Y	EP,A,0 531 257 (CIBA-GEIGY AG) 10 March 1993 see abstract; figure 1 ---	1-3,5, 7-9
A,P	EP,A,0 679 443 (BESPAK PLC) 2 November 1995 see column 5, line 37 - line 45 see column 8, line 10 - line 16; figures 1-6 ---	1-3,7-9
A	EP,A,0 569 611 (SIEMENS AG) 18 November 1993 see figure 2 ---	6 -/-

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Inter. [REDACTED] Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 00195 (HABLEY MED. CORP.) 5 January 1995 see abstract; figure 2 ---	1
A	EP,A,0 546 607 (GLAXO GROUP LTD.) 16 June 1993 see abstract; figures -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4770323	13-09-88	FR-A-	2593147	24-07-87
		EP-A-	0236152	09-09-87
		JP-A-	62168865	25-07-87
EP-A-531257	10-03-93	JP-A-	5192380	03-08-93
EP-A-679443	02-11-95	CA-A-	2147566	27-10-95
		JP-A-	8049649	20-02-96
		US-A-	5509578	23-04-96
EP-A-569611	18-11-93	EP-A-	0739654	30-10-96
WO-A-9500195	05-01-95	AU-A-	4642393	17-01-95
EP-A-546607	16-06-93	AU-B-	663535	12-10-95
		AU-A-	2979092	10-06-93
		BE-A-	1005867	22-02-94
		BR-A-	9204653	08-06-93
		CA-A-	2084350	04-06-93
		CN-A-	1078647	24-11-93
		CZ-A-	9203540	18-05-94
		DE-U-	9216359	01-04-93
		ES-A-	2049675	16-04-94
		FI-A-	925477	04-06-93
		FR-A-	2684304	04-06-93
		GB-A,B	2262138	09-06-93
		GR-A-	92100534	31-08-93
		HU-A,B	66577	28-12-94
		IL-A-	103945	31-12-95
		IT-B-	1256696	12-12-95
		JP-A-	6070980	15-03-94
		LU-A-	88193	17-08-93
		NZ-A-	245337	26-05-95
		PT-A-	101106	30-06-94
		SK-A-	354092	12-04-95
		US-A-	5307953	03-05-94
		ZA-A-	9209335	02-08-93